IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of Anderson	Confirmation No. 7327
Serial No. 09/994,937	Group Art Unit 1616
Filed November 28, 2001	Examiner Abigail Fisher

For SOLVENT SYSTEMS FOR PHARMACEUTICAL AGENTS

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

DECLARATION OF DAVID M. ANDERSON UNDER 37 C.F.R. 1.132

David M. Anderson declares as follows:

1. I am the inventor of the above-identified application. I hold a position in Lyotropic Therapeutics, Inc., the assignee of record of the above-identified application, as Vice President Scientific Affairs. I have read and understand the application, and I have read and understand the office action mailed June 16, 2009. I have also read and understand the references of record.

2. I have previously submitted Declarations in this case, including those filed on October 14, 2008 and March 26, 2009, and the declarations I made therein about my experience, education, qualifications and expertise remain accurate and true. As established in these prior declarations, I am an expert in the fields of chemical formulations and drug delivery, particularly as applied to structured fluids including emulsions, liposomes, lyotropic liquids and lyotropic liquid crystals, including reversed cubic and reversed hexagonal phase materials and stabilized dispersions thereof, and the like. Based on my education, training and experience, I am qualified to provide opinion evidence on the level of skill of one of ordinary skill in the art, and as to what would be obvious or not obvious to one of ordinary skill in the art. In addition, I am qualified and

equipped to conduct experiments and to provide test results relating to various pharmaceutical formulations.

3. I have reviewed the prior art cited by the Examiner in the Office Action, and in particular the Anderson, Engstrom and Unger patents cited by the Examiner. I am the inventor of the Anderson reference cited in the Office Action, and I am particularly informed and aware of the differences between the claimed invention in the pending case and that which is taught in and that which would be obvious to one of ordinary skill in the art having full knowledge of the Anderson reference. Similarly, my careful review of the Engstrom and Unger patents has informed me of the differences between the claimed invention in the pending case and that which would be obvious to one of ordinary skill in the art having full knowledge of both the Engstrom and Unger patents.

4. Experiments conducted by me or under my direct supervision, such as those presented in Exhibit 5 of the Declaration filed March 26, 2009, show that the inclusion of an essential oil (or component thereof) or tocopherol in the reversed cubic phase material of the present invention results in high stable loadings (e.g. from about 3% up to about 4.2%) of difficult to solubilize pharmaceutical agents in the reversed cubic phase material. Further, the presence of the essential oil (or component thereof) or tocopherol is necessary for the formation of the reversed cubic phase and for these high levels of loading to occur. That is, without the presence of tocopherol or essential oil, these compositions of water, phospholipid, and a difficult to solubilize pharmaceutical do not form reversed cubic phase material, nor do they containhigh loadings of difficult to solubilize pharmaceuticals in a reverse cubic phase structured fluid.

5. Confirmatory experiments conducted by me or under my direct supervision have demonstrated that the components taught in Example 36 of Anderson, when combined, do not form reversed cubic phase material. Rather, a liquid phase is formed. This is stated in the first sentence of Example 36, and, confirmatory experiments repeating that which is described in Example 36 have confirmed that a liquid phase is formed, not a reversed cubic phase. Hence, while the wording in Example 36 may not be

as artful as desired, any interpretation that Example 36 teaches a reversed cubic phase is simply incorrect.

6. Example 37 of Anderson teaches the formation of a microparticle dispersion, and does not teach the formation of a composition containing a reversed cubic phase structured fluid made from water, phospholipid, essential oil or a component thereof or tocopherol, and a difficult to solubilize pharmaceutical. Anisole is a synthetic compound which is not an essential oil or component thereof and is no way equivalent to tocopherol. (See Attachment) Furthermore, the Example notes that the liquid crystalline material formed was metastable. The composition in Example 36 also was metastable, and the consequences are discussed in Example 36. The incorporation of drug in the material is transient and is not sustained, but rather rapidly precipitates into surrounding liquid phase, leaving only a very low loading of drug incorporated in the reversed cubic phase material. By contrast, the present Invention overcomes these dual limitations presented in Examples 36 and 37, describing compositions which incorporate active agents in the reversed cubic phase material at high loadings.

7. During the Examiner's Interview which took place on December 10, 2009, the attached phase diagrams were discussed. It was hypothetically questioned during the interview what would happen if and essential oil or tocopherol was added the cubic phase material of Engstrom (it being recognized that Engstrom shows no such combination and that nothing in Engstrom teaches or suggests the use of essential oils or tocopherol as solubilizing agents useful for solubilizing difficult to solubilize drugs into reverse cubic phase materials. As indicated during the interview, based on my experience, it is my expert opinion that typically the addition of an essential oil (or component thereof) or tocopherol to the monoglyceride – phospholipid – water cubic phase material described by Engstrom would either 1) not be possible (i.e. the essential oil (or component thereof) or tocopherol would not substantially be taken up by and incorporated into the cubic phase material described by Engstrom); or 2) if taken up, would destroy (e.g. liquefy) the cubic phase nanostructure of the material.

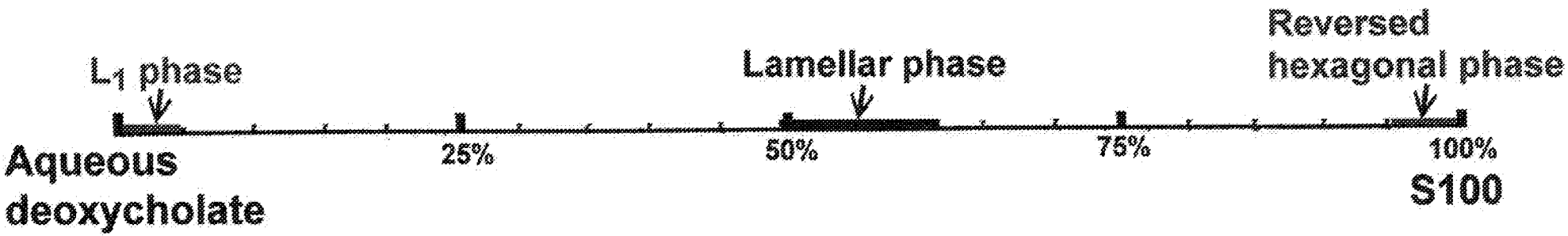
8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

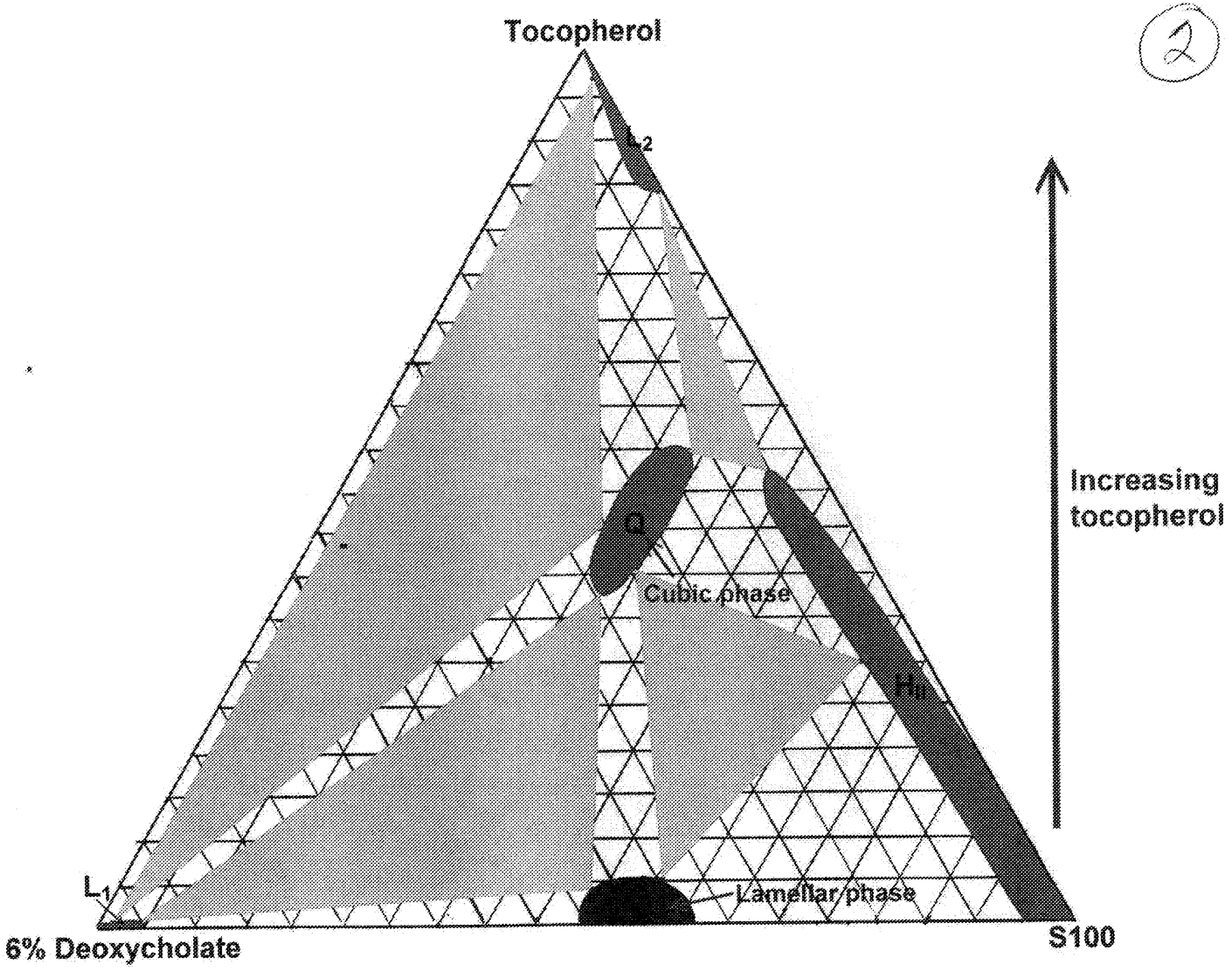
David M. Anderson, Ph.D.

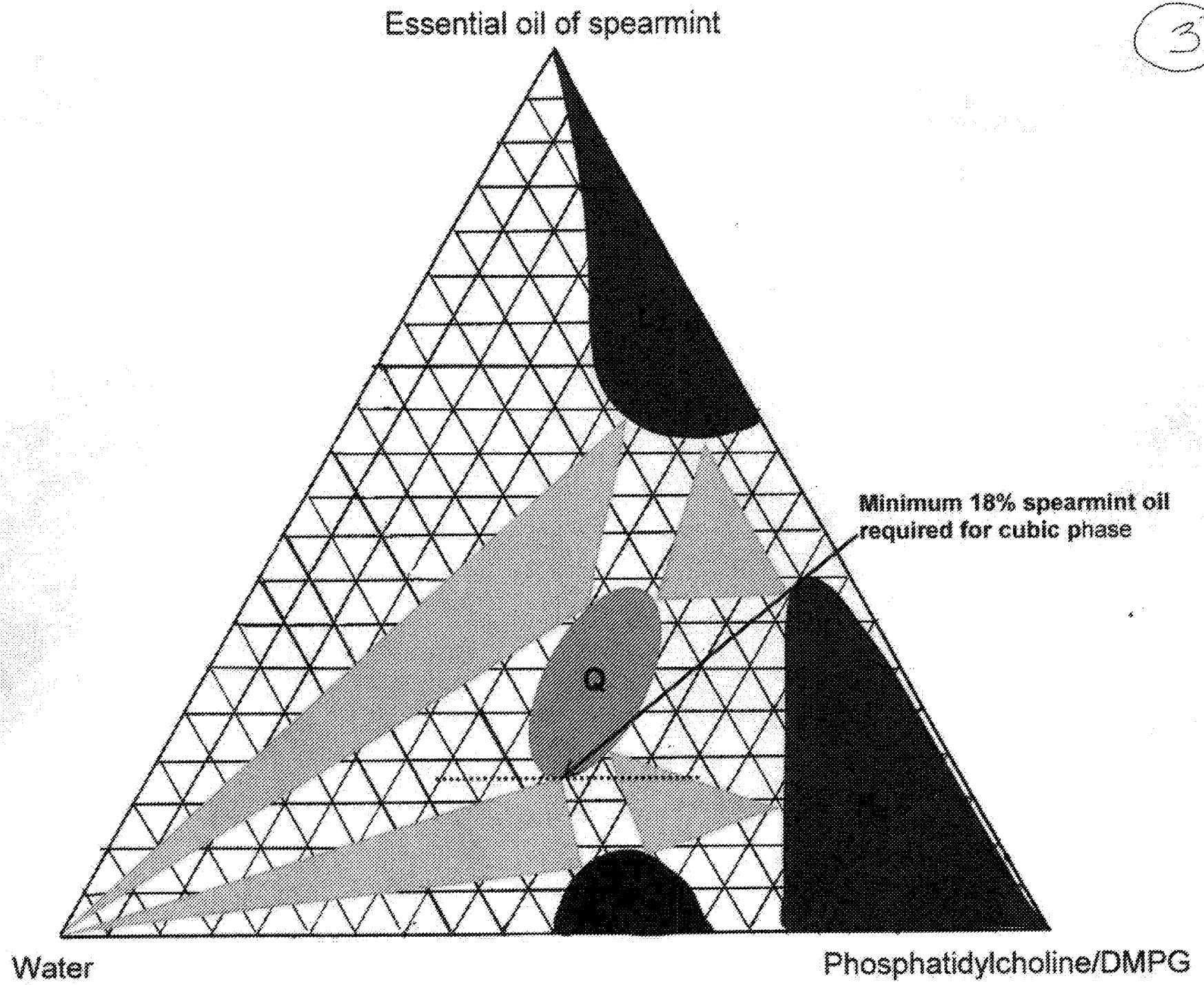
Dec. 14, 2009

Date

Phospholipid - Aqueous phase phase diagram: No tocopherol present



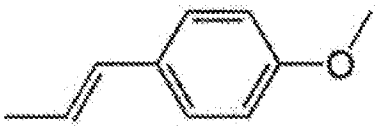

Tocopherol
L_2
Q
Cubic phase
H_{II}
Lamellar phase
L_1
6% Deoxycholate
S100
Increasing tocopherol


Essential oil of spearmint
Minimum 18% spearmint oil required for cubic phase
Q
Water
Phosphatidylcholine/DMPG

Anethole

From Wikipedia, the free encyclopedia

Anethole (also **para methoxy phenyl propene**, **p-propenylanisole**, and **isoestragole**) is an aromatic compound that occurs widely in nature, in essential oils. It contributes a large component of the distinctive flavors of anise and fennel (both in the botanical family Apiaceae), anise myrtle (Myrtaceae), licorice (Fabaceae), and star anise (Illiciaceae). Closely related to anethole is its double-bond isomer estragole, abundant in tarragon (Asteraceae) and basil (Lamiaceae), that has a flavor reminiscent of anise. Anethole has numerous commercial uses in multiple industries, and high potential for additional uses.

Anethole	
	
IUPAC name	1-methoxy-4-(1-propenyl)benzene
Identifiers	
CAS number	104-46-1 ✓
PubChem	637563
SMILES	O(c1ccc(\C=C\C)cc1)C
InChI	1/C10H12O/c1-3-4-9-5-7-10(11-2)8-6-9/h3-8H,1-2H3/b4-3+
InChI key	RUVINXPYWBROJD-ONEGZZNKBR
ChemSpider ID	553166
Properties	
Molecular formula	$C_{10}H_{12}O$
Molar mass	148.2 g mol^{-1}
Density	0.998 g/cm^3
Melting point	20-21 °C
Boiling point	234 °C; 81 °C at 2 mmHg
Hazards	
MSDS	External MSDS (http://physchem.ox.ac.uk/MSDS/AN/anethole.html)
Related compounds	
Related compounds	Anisole; Estragole
✓ (what is this?) (verify) (http://en.wikipedia.org/w/index.php?title=Anethole&diff=cur&oldid=321809583) Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	

Contents

Structure and properties

Chemically, anethole is an aromatic, unsaturated ether. It has two cis-trans isomers (see also E-Z notation), involving the double bond outside the ring. The more abundant isomer, and the one preferred for use, is the *trans* or *E* isomer: ***trans*-anethole**, **t-anethole**, **(E)-anethole**, **trans-para methoxy phenyl propene**. Its full chemical name is *trans*-1-methoxy-4-(prop-1-enyl)benzene.

Anethole is less soluble in water than in ethanol, which causes certain anise-flavored liquours to become opaque when diluted with water (see Ouzo effect). It is a clear, colorless liquid with boiling point 234 °C

and congealing point (freezing point) 20 °C;[1] below its congealing point, anethole forms white crystals. The crystals will precipitate from an aqueous solution, which causes a "snow globe" effect when certain anise-flavored liquours are chilled. This effect is the basis of a patent for industrial purification of anethole from sources such as pine oil.[2] Anethole can be crystallized directly from a source essential oil by lowering the temperature of the oil; adding a crystal of anethole helps to start the process.[3] Historically, this was used to detect adulteration.[4]

Production

Commercial sources of anethole include some essential oils:[5]

Essential oil	World production	*trans*-anethole
Anise	8 tons (1999)	95%
Star anise	400 tons (1999), mostly from China	87%
Fennel	25 tons (1999), mostly from Spain	70%

Uses

Anethole is a flavoring substance of commercial value. In addition, it is distinctly sweet, measuring 13 times sweeter than sugar. It is perceived as being pleasant to the taste even at higher concentrations. It is unrelated to glycyrrhizic acid, which often co-occurs with it, and also is very sweet. Anethole is used in alcoholic drinks, seasoning and confectionery applications, oral hygiene products, and in small quantities in natural berry flavors.[5]

Anethole is an inexpensive chemical precursor for paramethoxyamphetamine (PMA),[6] and used in its clandestine manufacture.[7] Anethole is present in the essential oil from guarana, which is alleged to have has a psychoactive effect; however, the absence of PMA or any other known psychoactive derivative of anethole leads to the conclusion that any purported psychoactive effect of guarana is not due to anethole.[8] Anethole is also present in absinthe, a liquor with a reputation for psychoactive effects; these effects however are attributed to ethanol[9] (see also Thujone).

Pharmaceutical drugs derived from or related to anethole include anisyldithiolthione,[10] anethole dithione (ADT), and anethole trithione (ATT).

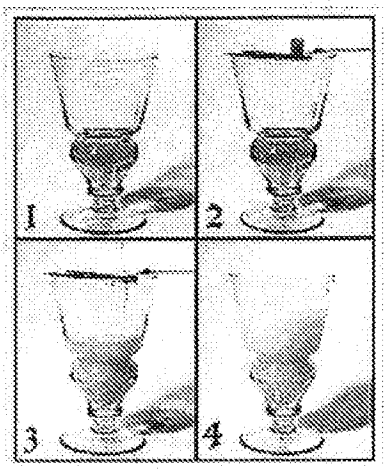
Research

Anethole is responsible for the "ouzo effect", the spontaneous formation of a microemulsion[11][12] that gives many alcoholic beverages containing anethole and water their cloudy appearance. Such a spontaneous microemulsion has many potential commercial applications in the food and pharmaceutical industries.[13] A derivative of anethole, anethole trithione, is being investigated for use in self-microemulsifying drug delivery systems (SMEDDS).[14]

Bacterial strains capable of using trans-anethole as the sole carbon source include JYR-1 (*Pseudomonas putida*)[15] and TA13 (*Arthrobacter aurescens*).[16] Because they metabolize anethole into several aromatic chemical compounds, these bacteria are candidates for use in commercial bioconversion of

these valuable compounds from anethole and other phenylpropanoids. Compared to other industrial processes, such bioconversion may be less costly and more friendly to the environment.[16]

Anethole has potent antimicrobial properties, against bacteria, yeast, and fungi.[17] Reported antibacterial properties include both bacteriostatic and bactericidal action against *Salmonella enterica*[18] but not when used against *Salmonella* via a fumigation method.[19] Antifungal activity includes increasing the effectiveness of some other phytochemicals (eg polygodial) against *Saccharomyces cerevisiae* and *Candida albicans*;[20] this synergistic effect has potential medical uses.[21]



Diluting absinthe with water produces a spontaneous microemulsion (ouzo effect)

In vitro, anethole has antihelmintic action on eggs and larvae of the sheep gastrointestinal nematode *Haemonchus contortus*.[22] Anethole also has nematicidal activity against the plant nematode *Meloidogyne javanica* in vitro and in pots of cucumber seedlings.[23]

Anethole also is a promising insecticide. Several essential oils consisting mostly of anethole have insecticidal action against larvae of the mosquitos *Ochlerotatus caspius*[24] and Aedes aegypti.[25][26] Similarly, anethole itself is effective against the fungus gnat *Lycoriella ingenua* (Sciaridae)[27] and the mold mite *Tyrophagus putrescentiae*.[28] Against the mite, anethole is a slightly more effective pesticide than DEET but anisaldehyde, a related natural compound that occurs with anethole in many essential oils, is 14 times more effective.[28] The insecticidal action of anethole is greater as a fumigant than as a contact agent. (E)-anethole is highly effective as a fumigant against the cockroach *Blattella germanica*[29] and against adults of the weevils *Sitophilus oryzae*, *Callosobruchus chinensis* and beetle *Lasioderma serricorne*.[30]

As well as an insect pesticide, anethole is an effective insect repellent against mosquitos.[31]

Safety

Formerly generally recognized as safe (GRAS), after a hiatus anethole was reaffirmed by Flavor and Extract Manufacturers Association (FEMA) as GRAS.[32] The hiatus was due to concerns about liver toxicity and possible carcinogenic activity, reported in rats.[33] Anethole is associated with a slight increase in liver cancer in rats,[33] although the evidence is scant and generally regarded as evidence that anethole is *not* a carcinogen.[33][34] An evaluation of anethole by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) found its notable pharmacologic properties to be reduction in motor activity, lowering of body temperature, and hypnotic, analgesic, and anticonvulsant effects.[35] A subsequent evaluation by JECFA found some reason for concern re carcinogenicity but insufficient data.[36] At this time, the JECFA summary of these evaluations is that anethole has *no safety concern at current levels of intake when used as a flavoring agent*.[37]

In large quantities, anethole is slightly toxic and may act as an irritant.[38]

See also

- Category:Anise liqueurs and spirits
- List of liqueurs#Anise-flavored liqueurs
- Chavicol
- Safrole
- Fenchone

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External links

- Molecular Models from OUC: anethole (http://people.ouc.bc.ca/woodcock/molecule/modelfiles/anethole.html)

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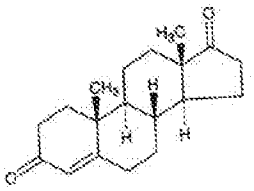
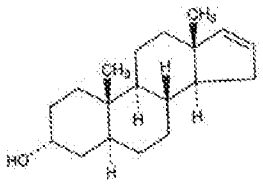


Dimorphous. Needles from acetone, mp 142-144°; crystals from hexane, mp 173-174°. $[\alpha]_D^{20}$ +191° (alc). uv max: 235 nm.

Dioxime, $C_{19}H_{28}N_2O_2$, crystals, mp 143°.

3-Semicarbazone, $C_{20}H_{31}N_3O_2$, crystals, dec 245°.

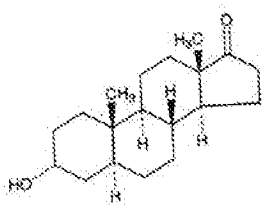
679. (3α,5α)-Androst-16-en-3-ol. 3α-Hydroxy-5α-androst-16-ene; Δ^{16}-androsten-3-ol. $C_{19}H_{30}O$; mol wt 274.45. C 83.15%, H 11.02%, O 5.83%. A major constituent of boar pheromone, having a pronounced musk-like odor. Isoln from swine testes: V. Prelog, L. Ruzicka, *Helv. Chim. Acta* **27**, 61 (1944). Prepn: V. Prelog *et al.*, *ibid.* 66; J. Fishman *et al.*, *J. Org. Chem.* **28**, 1443 (1963). Physiological role as a sex attractant for pigs: D. B. Gower, *J. Steroid Biochem.* **3**, 45 (1972). Use in pig artificial insemination: D. R. Melrose *et al.*, Ger. pat. **1,937,264** corresp to U.S. pat. **3,681,498** (1970, 1972 both to Nat. Res. Dev. Corp.). *In vivo* metabolism in boar testes: Y. A. Saat *et al.*, *Biochem. J.* **144**, 347 (1974). It has also been detected in human male axillary sweat, but has no androgenic activity: B. W. L. Brooksbank *et al.*, *Experientia* **30**, 864 (1974). Radioimmunoassay: D. C. Bickell, D. B. Gower, *J. Steroid Biochem.* **7**, 451 (1976). Receptor studies: J. N. Gennings *et al.*, *Biochim. Biophys. Acta* **496**, 547 (1977). Biosynthetic studies: E. L. Hurden *et al.*, *J. Endocrinol.* **81**, 161P (1979); G. M. Cook, D. B. Gower, *ibid.* **88**, 409 (1981). Discovery of the presence of androst-16-en-3-ol in truffles (*Tuber melanosporum*) has been offered as an explanation for the ability of pigs to detect truffles growing as deep as 1 meter underground: R. Claus *et al.*, *Experientia* **37**, 1178 (1981).



Crystals, mp 142.5-143°. Purified by sublimation in high vacuum and recryst from acetone. $[\alpha]_D^{18}$ +13.1° (c = 0.957 in chloroform). Gives a blue color in the Kägi-Miescher test, *cf. Helv. Chim. Acta* **22**, 683 (1939).

USE: As an aid to estrus determn in pig artificial insemination.

680. Androsterone. *(3α,5α)-3-Hydroxyandrostan-17-one*; *cis*-androsterone; 3α-hydroxy-17-androstanone; androstan-3α-ol-17-one; 3α-hydroxyetioallocholan-17-one; 3-epihydroxyetioallocholan-17-one. $C_{19}H_{30}O_2$; mol wt 290.45. C 78.57%, H 10.41%, O 11.02%. Isolation from male urine after removal of the phenolic estrogen fraction: Butenandt, Tscherning, *Z. Physiol. Chem.* **229**, 167 (1934); v. Euw, Reichstein, *Helv. Chim. Acta* **25**, 988 (1942). Prepn from cholesterol: Ruzicka, *ibid.* **17**, 1389 (1934); Marker, *J. Am. Chem. Soc.* **57**, 1755 (1935); Schoeller *et al.*, U.S. pat. **2,232,735** (1941 to Schering).



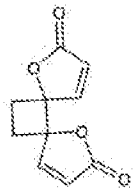
Crystals from acetone-ether, mp 185-185.5°. Sublimes in high vacuum. $[\alpha]_D^{18}$ +94.6° (c = 0.7 in abs alc). $[\alpha]_D^{25}$ +87.8° (c = 1.5 in dioxane). Not precipitated by digitonin. Barely soluble in water. Sol in most organic solvents.

Acetate, $C_{21}H_{32}O_3$, crystals from ether, sublimes in high vac, mp 165°. $[\alpha]_D^{24}$ +76.7° (c = 2.04 in dioxane); $[\alpha]_D^{25}$ +86° (c = 2 in ethanol).

Propionate, $C_{22}H_{34}O_3$, mp 151-152°.

Benzoate, $C_{26}H_{34}O_3$, mp 178°.

681. Anemonin. *trans-1,7-Dioxadispiro[4.0.4.2]dodeca-3,9-diene-2,8-dione*; 1,2-dihydroxy-1,2-cyclobutanediacrylic acid di-γ-lactone; Anemone camphor. Pulsatilla camphor. $C_{10}H_8O_4$; mol wt 192.17. C 62.50%, H 4.20%, O 33.30%. Found in *Anemone pulsatilla* L. and other *Ranunculaceae*. Its precursor in plants is protoanemonin. Isoln from *Ranunculus acer*: Zecher, Wohlmuth, *Sci. Pharm.* **22**, 95 (1954); *C.A.* **48**, 13169b (1954). Structure: Moriarty *et al.*, *J. Am. Chem. Soc.* **87**, 3251 (1965); Romain, *Diss. Abstr. B* **27**, 3867 (1967). Synthesis: Sugiyama *et al.*, *C.A.* **67**, 116604n (1967). Toxicity study: R. Brodersen, A. Kjaer, *Acta Pharmacol.* **2**, 109 (1946).



Crystals from petr ether, mp 157-158°. Volatile with steam. Slightly sol in cold, more in hot water; sol in hot alcohol, chloroform, alkalies with yellow color. Practically insol in ether. LD_{50} i.p. in mice: 150 mg/kg (Brodersen, Kjaer).

Note: Not to be confused with anemonine which is 5-(carboxymethyl)-1,1-dimethylimidazolium hydroxide inner salt.

682. Anethole. *1-Methoxy-4-(1-propenyl)benzene*; *p-propenylanisole*; anise camphor; Monasirup. $C_{10}H_{12}O$; mol wt 148.20. C 81.04%, H 8.16%, O 10.80%. Chief constituent of anise, star anise and fennel oils: Monad, de Dortan, *Ind. Parfum.* **5**, 401 (1950); Naves, Tucakov, *Compt. Rend.* **248**, 843 (1959). Separation of *cis* and *trans* isomers: Naves *et al.*, *ibid.* **246**, 1734 (1958); *Bull. Soc. Chim. France* **1958**, 566; Naves, *Helv. Chim. Acta* **43**, 230 (1960); Ferroni *et al.*, *Gazz. Chim. Ital.* **92**, 1198 (1962). Synthesis: Mueller, Köscheisen, *Ber.* **90**, 543 (1957); R. J. DePasquale, *Synth. Commun.* **10**, 225 (1980). Toxicity: J.-R. Boissier *et al.*, *Therapie* **22**, 309 (1967). *Review*: Wagner, *Mfg. Chemist* **23**, 56 (1952).

trans - isomer

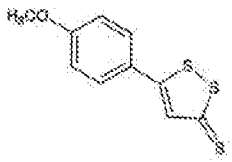
trans-Isomer, crystalline mass at 20-21°, mp 21.4°. Liquid above 23°. d_4^{20} 0.9883, $bp_{2.3}$ 81-81.5°. n_D^{20} 1.56145. uv max (ethanol): 259 nm (ε 22300). Practically insol in water. Misc with ether, chloroform; sol in benzene, ethyl acetate, acetone, carbon disulfide, petr ether; 1 ml dissolves in 2 ml alc. LD_{50} i.p. in rats: 900 mg/kg (Boissier).

cis-Isomer. d_4^{20} 0.9878, $bp_{2.3}$ 79-79.5°, n_D^{20} 1.55455. uv max (ethanol): 253.5 nm (ε 18500). LD_{50} i.p. in rats: 93 mg/kg (Boissier).

USE: Manuf anisaldehyde; flavoring agent; in perfumery, particularly for soap and dentifrices; sensitizer in bleaching colors in color photography; as an imbedding material in microscopy. Pharmaceutic aid (flavor).

THERAP CAT (VET): Has been used as a carminative.

683. Anethole Trithione. *5-(p-Methoxyphenyl)-3H-1,-2-dithiole-3-thione;* 3-(*p*-anisyl)trithione; 3-(*p*-methoxyphenyl)-4,5-dithiacyclopent-2-ene-1-thione; 3-(*p*-anisyl)-4,5-dithiacyclopent-2-ene-1-thione; (*p*-methoxyphenyl)trithiopropene; trithio-*p*-methoxyphenylpropene; 5-(*p*-methoxyphenyl)-1,2-dithiacyclopent-4-ene-3-thione; 3-(*p*-methoxyphenyl)trithione; trithioanethole; Heporal; Mucinol; Trithio; Sufralem; Tiotrifar; Felviten; Sulfegal; Sulfarlem. $C_{10}H_8OS_3$; mol wt 240.37. C 49.97%, H 3.35%, O 6.66%, S 40.02%. Prepn: Böttcher, Lüttringhaus, *Ann.* **557**, 89 (1947); Gaudin, Lozac'h, *Compt. Rend.* **224**, 557 (1947); Lüttringhaus *et al.*, *Ann.* **560**, 201 (1948); Gaudin, U.S. pats. **2,556,963, 2,688,620** (1951, 1954); Böttcher, Ger. pats. **855,865, 869,-799** and **874,447** (1952 and 1953); Thuiller, Vialle, *Bull. Soc. Chim. France* **1959**, 1398.



Orange-colored prisms from butyl acetate. Very bitter taste. mp 111°. Practically insol in water. Sol in pyridine, chloroform, benzene, dioxane, carbon disulfide. Slightly sol in ether, acetone, ethyl acetate, acetic acid, alc, cyclohexane, petr ether.

Oxime, $C_{10}H_9NO_2S_3$, yellow needles, mp 170°. Soluble in dioxane.

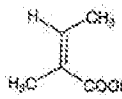
Methiodide, yellow crystals, mp 189°.

THERAP CAT: Choleretic.

684. Angelica. Fruit or root of *Angelica archangelica* L. (*A. officinalis* Moench.). *Umbelliferae. Habit.* Europe, Asia. *Constit.* Root: Volatile oil (0.3-1%), angelic acid, 6% resin, angelicol, angelicin, xanthotoxol, starch, osthole, osthenol, archangelicin, archangin, sitosterol, and acids such as aconitic, malic, quinic, chlorogenic, caffeic, fumaric, citric, angelic, and oxalic. Fruit: About 1% volatile oil, bitter substance, coumarins, resin. *Refs:* Späth, Festa, *Ber.* **67**, 853 (1934); Späth, Vierhapper, *ibid.* **70**, 248 (1937); Svendsen, *C.A.* **52**, 2173g (1958); Sroka, *Apoth.-Ztg.* **61**, 37 (1949).

THERAP CAT: Carminative, diaphoretic, diuretic.

685. Angelic Acid. *(Z)-2-Methyl-2-butenoic acid;* cis-2-dimethylcrotonic acid; 2-methylisocrotonic acid; cis-2,3-dimethylacrylic acid. $C_5H_8O_2$; mol wt 100.12. C 59.98%, H 8.05%, O 31.96%. Stereoisomer of tiglic acid. Found in ester form in sumbul root, *Angelica archangelica* L., *Umbelliferae* and together with tiglic acid esters in the oil of the Roman camomile, *Anthemis nobilis* L., *Compositae*. Isoln from seeds of *Schoenocaulon officinale* (Lindl.) A. Gray, *Liliaceae* (cevadilla seeds) by alkaline hydrolysis of cevadine: Stoll, Seebeck, *Helv. Chim. Acta* **35**, 1275 (1952). Synthesis by *trans* addition of bromine to tiglic acid: Buckles, Mock, *J. Org. Chem.* **15**, 680 (1950). Review and bibliography: Buckles *et al.*, *Chem. Rev.* **55**, 659 (1955).



Monoclinic rods, needles, plates; mp 45°. Spicy odor. *Vesicant.* d_4^{47} 0.983, bp_{760} 185°; bp_{12} 86°. Sublimes. Volatile with steam. n_D^{47} 1.4434. K at 25° = 5.0×10^{-5}. uv max (H_2O): 217 nm (ε 5.15×10^3). Molar heat of combustion 626.6 kcal. Sparingly soluble in cold water, freely sol in hot water. Sol in alcohol, ether. Prolonged boiling of aq soln causes isomerization to tiglic acid; the process is speeded up by traces of bromine and sunlight, also by strong mineral acids or alks. Dry crystals of angelic acid have been stored in bottles for years without evidence of isomerization.

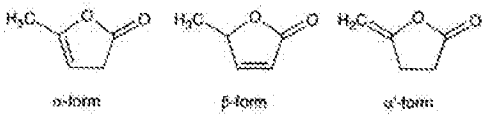
Calcium salt dihydrate, $Ca(C_5H_7O_2)_2 \cdot 3H_2O$, leaflets. Much more soluble in water than calcium tiglate: 100 parts of aq soln satd at 17.5° contains 23 parts of anhydr calcium angelate.

Amide, C_5H_9NO, crystals, mp 127-128°.

Methyl ester, $C_6H_{10}O_2$, liquid; d_4^{20} 0.9413; bp_{760} 128°; n_D^{20} 1.4321.

Ethyl ester, $C_7H_{12}O_2$, liquid; $d_4^{20.5}$ 0.9178; bp_{760} 141.5°, bp_{11} 49°. n_D^{20} 1.4304. Heat of formn at constant vol 963.1 kcal, at constant press. 964.2 kcal.

686. Angelica Lactone. *5-Methyl-2-furanone.* $C_5H_6O_2$; mol wt 98.10. C 61.22%, H 6.16%, O 32.62%. Exists in three forms. Prepn of α and β-forms: Wolff, *Ann.* **229**, 250 (1885); Thiele, *Ann.* **319**, 184 (1901); v. Auwers, *Ber.* **56**, 1672 (1923); J. H. Helberger *et al.*, *Ann.* **561**, 215 (1949). Prepn of α'-form: J. P. Wineburg *et al.*, *J. Heterocycl. Chem.* **12**, 749 (1975); V. Jäger, H. J. Günther, *Tetrahedron Letters* **1977**, 2543; R.A. Amos, J. A. Katzenellenbogen, *J. Org. Chem.* **43**, 560 (1978). Toxicity data for α-form: E. J. Moran *et al.*, *Drug Chem. Toxicol.* **3**, 249 (1980).



α-Form, *5-methyl-2(3H)-furanone, Δ²-angelica lactone, γ-methyl-α,γ-crotonolactone, 4-hydroxy-3-pentenoic acid γ-lactone.* Volatile needles, mp 18°. d_4^{20} 1.084. bp_{12} 56°. n_{He}^{20} 1.4476. One gram dissolves in 20 ml water at 15°. Heating with triethylamine soln converts it to the β-form. LD_{50} orally in mice: 2800 mg/kg (Moran).

β-Form, *5-methyl-2(5H)-furanone, Δ²-angelica lactone, γ-methyl-α,β-crotonolactone, 4-hydroxy-2-pentenoic acid γ-lactone.* Liquid. Not solidified at −17°. d_4^{20} 1.076. bp_{753} 208-209°. bp_{38} 87°. n_{He}^{20} 1.4603. Sol in water. Forms a dimer. More stable than α-form.

α'-Form, *dihydro-5-methylene-2(3H)-furanone, γ-methylene-γ-butyrolactone.* bp_{17} 80°.

687. Angiogenin. Single-chain, basic protein of 123 amino acids that induces the *in vivo* formation of blood vessels. Mol wt ~14,000 Da. First isolated from human adenocarcinoma cells; subsequently found in normal human plasma and shown to be produced by the liver. Angiogenin exhibits a characteristic ribonucleolytic activity toward 28S and 18S ribosomal RNA. Its amino acid sequence is 35% identical with that of human pancreatic ribonuclease. Isoln, characterization, and angiogenic activity: J. W. Fett *et al.*, *Biochemistry* **24**, 5480 (1985). Amino acid sequence: D. J. Strydom *et al.*, *ibid.* 5486. Cloning and DNA sequence of human angiogenin gene: K. Kurachi *et al.*, *ibid.* 5494. Structural study: K. A. Palmer *et al.*, *Proc. Nat. Acad. Sci. USA* **83**, 1965 (1986). Ribonucleolytic activity: R. Shapiro *et al.*, *Biochemistry* **25**, 3527 (1986). Isoln from normal human plasma: R. Shapiro *et al.*, *ibid.* **26**, 5141 (1987). Tissue distribution in neonatal and adult rats: H. L. Weiner *et al.*, *Science* **237**, 280 (1987); in human tumor and normal cells: S. M. Rybak *et al.*, *Biochem. Biophys. Res. Commun.* **146**, 1240 (1987). Inhibition of protein synthesis: D. K. St. Clair *et al.*, *Proc. Nat. Acad. Sci. USA* **84**, 8330 (1987). Inhibition of angiogenic and ribonucleolytic activities of angiogenin by placental ribonuclease inhibitor: R. Shapiro, B. L. Vallee, *ibid.* 2238; F. S. Lee, B. L. Vallee, *Biochemistry* **28**, 3556 (1989). *Reviews:* J. F. Riordan, B. L. Vallee, *Brit. J. Cancer* **57**, 587-590 (1988); B. L. Vallee, J. F. Riordan, *Adv. Exp. Med. Biol.* **234**, 41-53 (1988).

Anisole

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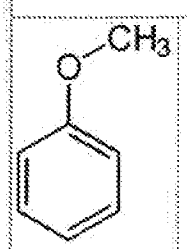
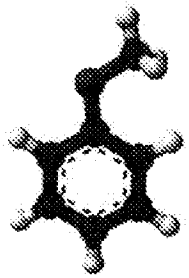
Anisole is the organic compound with the formula $CH_3OC_6H_5$. This colorless liquid has a smell reminiscent of anise seed. It is used as a precursor to other organic compounds. Substituted derivatives are also called anisoles.

Contents

Anisole	
	
IUPAC name	Anisole [2] (http://www.chemindustry.com/apps/chemicals?m=s&t=Anisole)
Other names	methoxybenzene and phenoxymethane
Identifiers	
CAS number	100-66-3 ✓
SMILES	COc1ccccc1
Properties	
Molecular formula	C_7H_8O
Molar mass	108.14 g/mol
Density	0.995 g/cm³
Melting point	−37 °C
Boiling point	154 °C
✓ (what is this?) (verify) (http://en.wikipedia.org/w/index.php?title=Anisole&diff=cur&oldid=305265640) Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	

Reactivity

Anisole undergoes electrophilic aromatic substitution reaction more quickly than does benzene, which in turn reacts more quickly than nitrobenzene. The methoxy group is an ortho/para directing group, which means that electrophilic substitution preferentially occurs at these three sites. The enhanced nucleophilicity of anisole vs benzene reflects the influence of the methoxy group, which renders the ring more electron-rich. The methoxy group strongly affects the pi cloud of the ring, moreso than the inductive effect of the electronegative oxygen.

Illustrative of its nucleophilicity, anisole reacts with acetic anhydride to give 4-methoxyacetophenone:

$$CH_3OC_6H_5 + (CH_3CO)_2O \rightarrow CH_3OC_6H_4C(O)CH_3 + CH_3CO_2H$$

Unlike most aromatic compounds and reflecting its high reactivity, the methoxyacetophenone undergoes a second acylation:

$$CH_3OC_6H_4C(O)CH_3 + (CH_3CO)_2O \rightarrow CH_3OC_6H_3(C(O)CH_3)_2 + CH_3CO_2H$$

Many related reactions have been demonstrated. For example, P_4S_{10} converts anisole to Lawesson's reagent, $[(CH_3O_6H_4)PS_2]_2$.

The ether linkage is highly stable, but the methyl group can be removed with hydroiodic acid:

$$CH_3OC_6H_5 + HI \rightarrow HOC_6H_4C(O)CH_3 + CH_3I$$

Preparation

Anisole is prepared by the Williamson ether synthesis, reacting sodium phenoxide with a methyl bromide and related reagents:[1]

$$2\ PhO^-Na^+ + CH_3Br \rightarrow CH_3OC_6H_5 + NaBr$$

Applications

Anisole is a precursor to perfumes, insect pheromones, and pharmaceuticals.[2] For example, synthetic anethole is prepared from anisole.

Safety

Anisole is relatively nontoxic with LD50 of 3700 mg/kg in rats.[3]

See also

- Anethole
- Bromoanisole
- Butylated hydroxyanisole
- Ether
- Ethyl phenyl ether
- Phenol
- 2,4,6-Trichloroanisole (cork taint)

References

1. ^ G. S. Hiers and F. D. Hager (1941), "Anisole (http://www.orgsyn.org/orgsyn/orgsyn/prepContent.asp?prep=cv1p0058) ", *Org. Synth.*, http://www.orgsyn.org/orgsyn/orgsyn/prepContent.asp?prep=cv1p0058; *Coll. Vol.* **1**: 58
2. ^ Helmut Fiege, Heinz-Werner Voges, Toshikazu Hamamoto, Sumio Umemura, Tadao Iwata, Hisaya Miki6, Yasuhiro Fujita, Hans-Josef Buysch, Dorothea Garbe, Wilfried Paulus "Phenol Derivatives" in Ullmann's Encyclopedia of Industrial Chemistry, 2002, Wiley-VCH, Weinheim. doi:10.1002/14356007.a19_313 (http://dx.doi.org/10.1002%2F14356007.a19_313)
3. ^ MSDS.[1] (http://www.seas.upenn.edu/~nanofab/chemicals/MSDS_Solvent_Anisole.pdf)

External links

- International Chemical Safety Card 1014 (http://www.inchem.org/documents/icsc/icsc/eics1014.htm)
- Pherobase (http://www.pherobase.com/database/compound/compounds-detail-anisole.php) pheromone database entry

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Categories: Flavors | Ethers | Aromatic compounds | Pheromones

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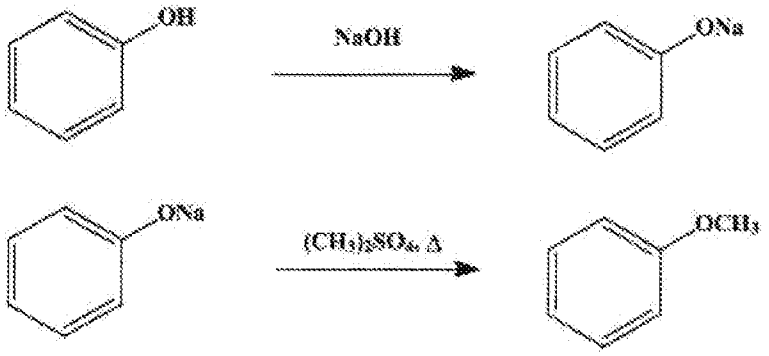
Organic Syntheses, Coll. Vol. 1, p.58 (1941); Vol. 9, p.12 (1929).

ANISOLE



Submitted by G. S. Hiers and F. D. Hager.
Checked by Henry Gilman, S. A. Harris, and G. F. Wright.

1. Procedure

In a 5-l., three-necked, round-bottomed flask fitted with an efficient stirrer, separatory funnel, and reflux condenser is placed a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide (Note 1) in 1 l. of water. The mixture is cooled, with stirring, in an ice-salt bath to below 10°. There is then added through the separatory funnel, with stirring, 315 g. (235 cc., 2.5 moles) of dimethyl sulfate (Note 2). This addition requires about one hour, and the cooling bath is not removed until the addition is complete. The mixture is then heated on a water bath for one-half hour. At the end of this time there is added through the separatory funnel a mixture of 235 g. (2.5 moles) of phenol and 100 g. (2.5 moles) of sodium hydroxide in 1 l. of water. This addition requires about fifteen minutes. The mixture is then refluxed vigorously over a free flame for fifteen hours (Note 3).

The mixture is cooled and the anisole layer is separated. The aqueous portion is extracted with about 200 cc. of benzene (Note 4). The combined anisole-benzene portion is washed once with water, dried over calcium chloride and distilled from a modified Claisen flask (p. 130). The portion boiling at 100–153° is refractionated. The main fraction distils at 153–154°/748 mm. The yield is 388–405 g. (72–75 per cent of the theoretical amount) (Note 5) and (Note 6).

2. Notes

1. The sodium hydroxide was a high quality technical grade.

2. Dimethyl sulfate is toxic, but with due care to avoid spattering of the liquid and inhaling of the vapor the operation may be carried out without the use of a hood. Ammonia is a specific antidote for dimethyl sulfate and should be kept at hand to destroy any of the ester accidentally spilled.

A good technical grade of dimethyl sulfate was used.

3. When the period of refluxing is shorter, the yield is materially decreased. The first methyl group reacts easily but the second only with considerable difficulty. A longer period of refluxing does not give much larger yields. As the sodium sulfate concentration increases, the dimethyl sulfate hydrolyzes less readily.

It is recommended that the addition of dimethyl sulfate is best effected at the lowest temperature where reaction takes place readily. With phenol this is 25–35°. For

the second methyl group, the mixture is not refluxed but the anisole is boiled out, during which time the reaction completes itself (W. W. Hartman, private communication).

4. A separate fractional distillation of this benzene extract yields 9–18 g. of anisole. The major part of the anisole contained in the aqueous layer may be recovered by steam distillation instead of a benzene extraction. Neither method of recovery is wholly satisfactory.

5. When only one-half the amount of phenol is used, the yield is 85–92 per cent but with fairly inexpensive phenol it is more profitable to operate in such a manner that both methyl groups of the dimethyl sulfate are used.

6. Other methyl ethers may be prepared by a similar procedure. Methyl β-naphthyl ether is obtained in a 65–73 per cent yield by adding the dimethyl sulfate over a period of thirty minutes to equivalent quantities of β-naphthol and sodium hydroxide kept cool by an ice-water bath, then heating for one hour at 75–78°, and, finally, crystallizing from benzene to obtain the pure methyl ether which melts at 71°.

3. Discussion

Anisole can be prepared from phenol or its salts by the use of the following methylating agents: methyl chloride;[1] sodium methyl sulfate;[2] methyl alcohol in the presence of thorium oxide;[3] methyl alcohol and β-naphthalenesulfonic acid[4] or potassium hydrogen sulfate[5] or boron fluoride;[6] dimethyl sulfate;[7] and methyl ether and boron fluoride.[8]

References and Notes

1. Vincent, Bull. soc. chim. (2) **40**, 106 (1883).
2. Nollau and Daniels, J. Am. Chem. Soc. **36**, 1890 (1914).
3. Sabatier and Maihle, Compt. rend. **151**, 359 (1910).
4. Krafft and Roos, Ger. pat. 76,574 [Frdl. **4**, 17 (1894–97)]; Rodionow, Bull. soc. chim. (4) **45**, 118 (1929); Terlinck, Ing. chim. **8**, 233 (1924) [C. A. **21**, 1978 (1927)].
5. Aktien-Gesellschaft für Anilin-Fabrikation, Ger. pat. 23,775 [Frdl. **1**, 43 (1877–87)].
6. Sowa, Hennion, and Nieuwland, J. Am. Chem. Soc. **57**, 709 (1935).
7. Lewis, Shaffer, Trieschmann, and Cogan, Ind. Eng. Chem. **22**, 34 (1930); Wolford, ibid. **22**, 397 (1930); Hodgson and Nixon, J. Chem. Soc. 2166 (1930).
8. Kolka and Vogt, J. Am. Chem. Soc. **61**, 1463 (1939).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

anisole-benzene

calcium chloride (10043-52-4)

ammonia (7664-41-7)

Benzene (71-43-2)

methyl alcohol (67-56-1)

sodium hydroxide (1310-73-2)

phenol (108-95-2)

sodium sulfate (7757-82-6)

β-naphthol (135-19-3)
Anisole (100-66-3)
dimethyl sulfate (77-78-1)
Methyl β-naphthyl ether (93-04-9)
methyl ether (115-10-6)
methyl chloride (74-87-3)
sodium methyl sulfate (512-42-5)
thorium oxide
β-naphthalenesulfonic acid (120-18-3)
potassium hydrogen sulfate (7646-93-7)
boron fluoride (7637-07-2)

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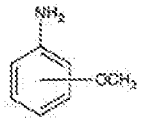


***m*-Anisidine, 3-methoxybenzenamine, 3-methoxyaniline, 3-aminoanisole.** Pale yellow, oily liquid. Remains fluid even at −10°. bp 251°, bp_2 81-86°. Sparingly sol in water; sol in alc, acids.

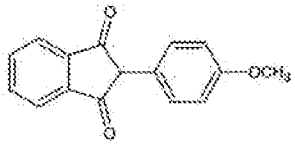
***o*-Anisidine, 2-methoxybenzenamine.** Yellowish liquid; becomes brownish on exposure to air. Volatile with steam. bp 225°, mp +5°. d_{15}^{15} 1.098. Practically insol in water. Miscible with alc, ether. *Keep well closed and protected from light.*

***p*-Anisidine, 4-methoxybenzenamine.** Crystals, mp 57°, bp 246°. Sparingly sol in water; freely sol in methanol, ethanol.

Note: *o*-Anisidine hydrochloride may reasonably be anticipated to be a carcinogen: *Seventh Annual Report on Carcinogens* (PB95-109781, 1994) p 93.

USE: In the manuf of azo dyes.

706. Anisindione. ***2-(4-Methoxyphenyl)-1H-indene-1,3(2H)-dione;*** 2-*p*-anisyl-1,3-indandione; 2-(*p*-methoxyphenyl)-1,3-indandione; SPE-2792; Miradon; Unidione. $C_{16}H_{12}O_3$; mol wt 252.27. C 76.18%, H 4.79%, O 19.03%. Prepn: Koelsch, *J. Am. Chem. Soc.* **58**, 1331 (1936); Horeau, Jacques, *Bull. Soc. Chim. France* **1948**, 53; Sperber, U.S. pat. **2,899,358** (1959 to Schering).



Pale yellow crystals from acetic acid or ethanol, mp 156-157°.

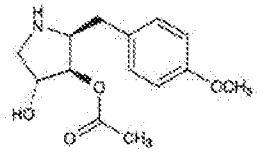
THERAP CAT: Anticoagulant.

707. Anisole. ***Methoxybenzene.*** C_7H_8O; mol wt 108.14. C 77.75%, H 7.46%, O 14.80%. $C_6H_5OCH_3$. Prepn from phenol and dimethyl sulfate: Ullmann, *Ann.* **327**, 114 (1903); Graebe, *Ann.* **340**, 204 (1905); G. S. Hiers, F. D. Hager, *Org. Syn.* **coll. vol. I**, 58 (2nd ed., 1941); from bromobenzene: Agfa, **Ger. pat. 411,052**; *Chem. Zentr.* **1925, I**, 2411; *Frdl.* **15**, 193; by passing methyl chloride into a suspension of sodium phenolate in liquid ammonia: White *et al., J. Am. Chem. Soc.* **46**, 965 (1924); from phenol, methyl iodide and potassium carbonate in dimethylformamide: Brieger *et al., J. Chem. Eng. Data* **13**, 581 (1968). Forms oils or resins by condensation with formaldehyde: **Ger. pats. 403,264; 406,152**; *Chem. Zentr.* **1925, I**, 307, 1816; *Frdl.* **14**, 626, 627. Absorption spectrum: Scheibe, *Ber.* **59**, 2625 (1926). Soly in glycerol, *see* McEwen, *J. Chem. Soc.* **123**, 2285 (1923). Toxicity studies: J. M. Taylor *et al., Toxicol. Appl. Pharmacol.* **6**, 378 (1964).

Liquid. Agreeable aromatic odor. d_4^{25} 0.9956; d_4^{25} 0.9701. mp −37.3°. bp_{760} 155.5°; bp_{100} 93.0°; bp_{50} 70.7°; bp_{20} 55.8°; bp_{10} 42.2°; bp_5 30.0°; $bp_{1.0}$ 5.4°. n_D^{20} 1.51791. Sol in alcohol and ether. Insol in water. LD_{50} orally in rats: 3700 mg/kg (Taylor).

USE: In perfumery, in organic syntheses.

708. Anisomycin. ***1,4,5-Trideoxy-1,4-imino-5-(4-methoxyphenyl)-D-xylo-pentitol 3-acetate; [2R-(2α,3α,4β)]-2-[(4-methoxyphenyl)methyl]-3,4-pyrrolidinediol 3-acetate;*** 2-*p*-methoxyphenylmethyl-3-acetoxy-4-hydroxypyrrolidine; Flagecidin. $C_{14}H_{19}NO_4$; mol wt 265.31. C 63.38%, H 7.22%, N 5.28%, O 24.12%. Protein synthesis inhibiting antibiotic isolated from *Streptomyces griseolus* and *S. roseochromogenes*: Sobin, Tanner, Jr., *J. Am. Chem. Soc.* **76**, 4053 (1954); Tanner *et al.*, U.S. pat. **2,691,618** (1954 to Pfizer). Activity: J. E. Lynch *et al., Antibiot. & Chemother.* **4**, 844, 899 (1954). Structure and stereochemistry: Beereboom *et al., J. Org. Chem.* **30**, 2334 (1965); Schaefer, Wheatley, *ibid.* **33**, 166 (1968); Butler, *ibid.* 2136. Biosynthesis: Butler, *ibid.* **31**, 317 (1966). Total synthesis: Oida, Ohki, *Chem. Pharm. Bull.* **16**, 2086 (1968); *ibid.* **17**, 1405 (1969); Felner, Schenker, *Helv. Chim. Acta* **53**, 754 (1970). Chiral synthesis: J. P. H. Verheyden *et al., Pure Appl. Chem.* **50**, 1363 (1978). Stereospecific total synthesis: D. P. Schumacher, S. S. Hall, *J. Am. Chem. Soc.* **104**, 6076 (1982). Mechanism of action: A. Jiménez, D. Vázquez in *Antibiotics* vol. 5(pt. 2), F. E. Hahn, Ed. (Springer-Verlag, New York, 1979) pp 1-19. Solubility and stability data: *Antibiot. Ann.* **1954-55**, pp 809-810. Prepn of deacetylanisomycin from anisomycin: Nickell *et al.*, U.S. pat. **2,935,444** (1960 to Pfizer).



Long needles from ethyl acetate or water, mp 140-141° $[\alpha]_D^{25}$ −30° (methanol). uv max: 324, 277, 283 nm (ε 10800, 1800, 1600). Base is moderately sol in water; sol in lower alcohols, esters, ketones, chloroform; slightly sol in benzene, toluene and hexane. Aq solns are stable over a wide pH range at room temp.

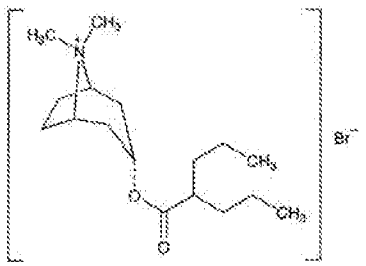
Hydrochloride, $C_{14}H_{19}NO_4.HCl$, crystals from ethyl acetate + ethanol, mp 187-188°. Very sol in water.

Deacetylanisomycin, $C_{12}H_{17}NO_3$, mp 176-179°. $[\alpha]_D^{25}$ −20.0° (methanol). pK 9.2.

USE: Anisomycin and deacetylanisomycin in the eradication of bean mildew; to inhibit other pathogenic fungi in plants.

THERAP CAT: Antiprotozoal (Trichomonas).

709. Anisotropine Methylbromide. ***endo-8,8-Dimethyl-3-[(1-oxo-2-propylpentyl)oxy]-8-azoniabicyclo[3.2.1]octane bromide; 3α-hydroxy-8-methyl-1αH,5αH-tropanium bromide 2-propylvalerate;*** 8-methyltropinium bromide 2-propylvalerate; 8-methyl-3-(2-propylpentanoyloxy)tropinium bromide; octatropine methylbromide; Lytispasm; Valpin. $C_{17}H_{32}BrNO_2$; mol wt 362.35. C 56.35%, H 8.90%, Br 22.05%, N 3.87%, O 8.83%. Prepn: Weiner, Gordon, U.S. pat. **2,962,499** (1960 to Endo Labs.). Metabolism: Shindo *et al., Chem. Pharm. Bull.* **19**, 513 (1971).



Crystals from acetone, mp 329°.

Methyl chloride, $C_{17}H_{32}ClNO_2$, crystals from acetone, mp 289°.

THERAP CAT: Anticholinergic.

710. *o*-(*p*-Anisoyl)benzoic Acid. ***2-(4-Methoxybenzoyl)benzoic acid;*** S-23/46. $C_{15}H_{12}O_4$; mol wt 256.26. C 70.31%, H 4.72%, O 24.97%. Prepn from phthalic anhydride and anisole: Meyer, Turnau, *Monatsh.* **30**, 486 (1909). Alternate route: Arcus, Marks, *J. Chem. Soc.* **1956**, 1627.